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HAROLD WARD DUDLEY

1887—1935

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Howard D. Kelley



HAROLD WARD DUDLEY 1887-1935

By the untimely death of HAROLD WARD DUDLEY, before he had completed his 48th year, Science has lost a devoted servant and a distinguished investigator. The wide influence which he had acquired, especially among those concerned with biochemistry, was due to his fine character and his personal charm, as well as to his already brilliant record of research; and his services to the remarkable development of that branch of Science in this country, apart from the direct effect of his own investigations, involved a quiet and unselfish devotion of time and work to the interests of his colleagues.

Dudley was born at Derby on October 30, 1887, the eldest son of the late Rev. Joshua Dudley, who, as a Methodist minister, was stationed for successive periods in different parts of the country. Harold Dudley's schooling changed with these movements of his home. He was at Truro College, and at the King Edward VI Grammar School, Morpeth, from which he entered Leeds University, taking Chemistry as his subject, and specializing in Organic Chemistry. This brought him under the influence of the late J. B. Cohen, F.R.S., who died earlier in this year (*see* Obituary Notice, p. 503 of this issue). Cohen was not only a great and inspiring teacher; there must have been something in his teaching of Organic Chemistry which aroused interest in its biological significance to account for the number of his pupils who have won success and distinction in biochemistry. It is sufficient to name, in order of seniority, Dakin, Raper, Hartley, Dudley, Woodman, Raistrick, and Wormall, and to note that four of these have been elected to our Fellowship for their work in biochemistry, to realize that the teaching of Cohen, himself no biologist, has had, through his pupils, a powerful influence on the development of this relatively young department of Science. Dudley, after graduation in Chemistry, began research under Cohen's guidance, and proceeded to the higher degree of M.Sc. with a thesis on "The Relation of Position Isomerism to Optical Activity in Certain Menthyl Esters." He was then awarded a Science Research Scholarship by the 1851 Commissioners, and, under Cohen's advice, went to Emil Fischer's famous Institute in Berlin. There he worked with Professor Wilhelm Traube on the chemistry of the purines, and took the degree of Ph.D. in 1912.

When Dudley returned to England, there came to him an opportunity which had a decisive influence on his career. The late Dr. Christian Herter, of New York, had equipped the top floor of his house in Madison

Avenue as a laboratory for research in medical and biological chemistry. H. D. Dakin, who had been invited by Herter to work in this private laboratory, had been engaged there since 1905 in fundamental researches in biochemistry, and remained in charge of the laboratory after Herter's early death in 1910. In 1912 he was seeking an assistant and collaborator, and through his old teacher Cohen was brought into touch with Dudley. The appointment was offered and accepted, and Dudley entered upon two years of happy, intimate, and fruitful collaboration with Dakin, who already had problems of great interest awaiting further development. These joint researches belong mainly to two groups. One group was concerned with the function of glyoxals in the metabolism of carbohydrates, and in the intermediary metabolism of carbohydrates and amino-acids. In this connexion Dakin and Dudley discovered the tissue enzyme glyoxalase, and devised a method of measuring its activity by following the conversion of phenyl-glyoxal into mandelic acid.

The other group was concerned with the partial racemization of proteins by treatment with warm alkali. When the constituent amino-acids were separated from such racemized proteins by acid hydrolysis, it was found that only some of them had undergone racemization, and theoretical grounds were given for the view that these were the terminal members of the peptide chains from which the complex molecules were built. A further observation of great interest was that a protein which had been thus treated, until the racemization process had reached its end point, was completely refractory to digestion by proteolytic enzymes, and behaved in the body like an inert substance, passing rapidly through the kidney into the urine. Experiments made by Ten Broek showed that it had completely lost its antigenic properties.

Dudley's two years in New York had given him a wealth of experience and of ideas, in the subject which was now to be his life's work. He had made many pleasant personal contacts in scientific circles in America; and he had formed a close and lasting friendship with Dakin and with Mrs. Herter (now Mrs. Dakin) and her family. He was ripe for independent activity when he returned to Leeds, in 1914, as Lecturer in Biochemistry in the Animal Nutrition Research Institute. Here he was quickly engaged with problems arising from his work with Dakin, as shown by papers, published in 1915, on the estimation of glyoxalase in blood, and, jointly with H. E. Woodman, on the caseins of cow's and sheep's milk. No difference could be found between these two proteins, as regards the nature of the amino-acids constituting them or the proportions in which these were present. Application of the racemization method, however, revealed a clear difference between the amino-acids

which became racemized in the two cases, indicating a specific difference of their arrangement in the respective molecules. Dudley realized the possible significance of this for the explanation of antigenic specificity, and arranged with Ten Broek for tests, which showed that the anaphylactic reaction would discriminate between these two caseins. This relation between antigenic specificity and the arrangement of the amino-acids forming the molecule was later confirmed, and perhaps more clearly defined, in a comparison made by Dakin and myself on the crystallized egg albumins of the hen and the duck ; but the conception had been first put to the test in the case of the two caseins, with a positive result, on Dudley's initiative.

The outbreak of war soon terminated Dudley's work at Leeds. He obtained a commission in the army, and was detailed for special work on protection against the new chemical weapons of war, which he performed with characteristic thoroughness under the late Professor Starling, and subsequently under the late Brigadier-General Harrison, at the R.A.M. College at Millbank. Early in 1918, having been promoted to the rank of major, he was sent to the United States of America, where his thorough knowledge of the British experience, his acquaintance with American conditions, and his many personal contacts in that country, specially qualified him for an advisory mission to the new anti-gas organization of the American army and its mechanism of supply.

When the end of the war came, Dudley, whose services were recognized by the award of the O.B.E., was ready and eager to return to his normal activity in research. I was reorganizing the Department of Biochemistry and Pharmacology under the Medical Research Council, in preparation for its transfer, from war-time quarters in the Lister Institute, to its permanent home in the National Institute for Medical Research at Hampstead, which had been occupied throughout the war as a military hospital. My first colleague in the department, George Barger, had already left to take the new Chair of Medical Chemistry in Edinburgh. The needs of the future suggested the appointment of two younger men, one to be concerned mainly with biochemistry in the stricter sense and the other with the chemistry of drugs and synthetic remedies. I was fortunate in finding Dudley and Harold King ready to accept appointment, and they joined our team together. There was much planning and organization to be done, in converting rooms which had originally been hospital wards, and in use as such until well into 1919, into experimental laboratories. The most extensive adaptation and equipment was required in the case of the chemical laboratories, and for this Dudley, with King's co-operation, made himself responsible. In later

years the equipment was much extended, and included a laboratory for extracting and concentrating materials on a semi-manufacturing scale, for which Dudley again took the chief responsibility.

While the initial minimum of equipment was being installed, up to the spring of 1920 research went on in our temporary quarters, and here Dudley carried out an important part of his work on the hormones of the pituitary posterior lobe. It had long been known that an extract from this organ had powerful stimulant effects on the muscular walls of the arteries and on that of the uterus. These had generally been regarded as two expressions of the activity of one principle. When Dudley undertook investigations on its chemical properties, and applied a method, then newly introduced by Dakin for the separation of amino-acids, in which the watery solution was continuously extracted by butyl alcohol, the substance acting on the uterus was completely extracted, while the pressor principle remained largely in the watery residue. The presence in this extract of two different substances, each responsible for one only of its principal activities, was for the first time made clear. The discovery was not unchallenged, and Dudley was involved with me in further work, some of it giving further information of interest, some of it disappointing; but no published item of Dudley's contribution has to my knowledge needed revision. By methods later found by Kamm and others, the two principles in the extract are now separated on a large scale, and offered in separate solutions for practical use in therapeutics; so that the correctness of Dudley's original observation is no longer in question.

During 1922 private information came from Toronto to the Medical Research Council of the rapid development of Banting and Best's discovery that the antidiabetic hormone, insulin, could be obtained by artificial extraction from the pancreas. The Council were invited to send scientific observers to report to them on the progress of this remarkable discovery, and on the initial results of its practical application. I was asked to undertake this mission of inquiry, and, at my request, Dudley was sent with me. We arrived at Toronto towards the end of September, 1922, and the evidence put before us carried immediate conviction that a genuine discovery of great potential importance had been made. The late Professor J. J. R. Macleod had organized a team of workers to reinforce the activities of the original discoverers, in work directed to the improvement of methods for estimating the amount of insulin present in extracts, and to the production of purer preparations in a higher yield. The practical production was, indeed, still in its infancy. The Toronto laboratory was working feverishly, with makeshift apparatus installed in a cellar, to keep pace with the demand for insulin for the continued

treatment of a few cases already receiving it. Dudley and I visited also the factory of Eli Lilly & Co., at Indianapolis, who had already, with much larger facilities, been co-operating with the Toronto workers in the effort to arrive at a large-scale production of insulin, in a suitably pure solution for therapeutic use. Though there was a clear promise of improvement with experience, there was no certainty as to its extent at the time of our visit. A yield of 5 "units" of insulin from a kilogramme of pancreas was still regarded as a good result; and the extract containing it was highly impure, of poor stability, and liable to lose a large part of its insulin during passage through a sterilizing filter. Dudley and I, in the Report which we wrote on the return voyage, could record our conviction of the importance of the scientific discovery, and of its success in practical therapeutics, so far as it had been applied; but, as to the possibility of making insulin generally available for the treatment of diabetes, in rich and poor alike, we could still only speculate. The practical decision, which the Medical Research Council had to make with our advice, was between waiting until supplies of insulin became available from Canada and America and an attempt to produce it immediately on an experimental basis in this country, and to accelerate its large-scale production here by manufacture. The latter choice meant the concentration of our work and interest, and of Dudley's especially, on a problem entirely new to us, which was the subject of very active researches in Canada and America, where the experience of many months was already available. It would have been easy for Dudley to suggest that we should only waste time if we tried to overtake that highly organized and rapidly progressing development. He chose, with me, to advise that we should let everything else give way to an effort to make insulin available in Britain as quickly as possible. Emergency arrangements were made for small-scale preparation to start in different hospitals, while Dudley worked, with his usual quiet efficiency, to find a process which would enable manufacturers to produce insulin on a scale, and at a price, which would bring it within the reach of all who needed it. He found that the conditions for its successful extraction did not depend, as had been supposed, on protecting it from trypsin, but on a reaction sufficiently far, on either side, from the isoelectric point of the hormone; he found that loss in filtration could be eliminated by adjustment of the reaction to an appropriate acidity; and he discovered a method, by separation as a picrate and reconversion into a hydrochloride, of purifying crude insulin and obtaining it in a dry, stable condition. Within a few months he could give to the manufacturers a process yielding 500 instead of 5 units of insulin from a kilogramme of the raw gland. I do not know

to what extent these discoveries of Dudley have survived in modern manufacture. It is certain that others as important were concurrently being made in Canada and America. What is also quite certain, however, is that British manufacture was enabled, by his devoted and concentrated activity, rapidly to overtake the effort on the other side of the Atlantic, so that the solution of the practical problem was in sight as early in this country as in any in the world. When, in 1923, an International Conference decided to adopt a stable standard preparation of insulin for world-wide use, and to define the unit in terms of it, Dudley was charged with the preparation of this first insulin standard. Apart from his chemical work on the nature of insulin, Dudley had to co-operate in the organization of biological tests for estimating its activity. Incidentally to this side of the work he gave, with Marrian, the first demonstration of the apparent paradox, that a mouse receiving an excessive dose of insulin, and dying with a rapid fall of its metabolism nearly to zero, is found to have lost practically the whole of its preformed carbohydrate. This was one of the starting-points of investigations, in many laboratories, on the nature of the action of insulin, including a series in which C. H. Best, one of the co-discoverers of insulin, later joined with other workers in my own laboratory.

Dudley now became interested in an entirely different problem. Otto Rosenheim, who had worked with Mrs. Rosenheim many years earlier on the curious base spermine, widely distributed in the tissues and still of unknown function, made contact with the Institute and with Dudley at a time when the demands of the insulin work were becoming less urgent. They embarked on a co-operative investigation which, with remarkable rapidity, led to the extraction of spermine on a scale enabling them to determine its curious and unexpected constitution— $\alpha\delta$ bis (γ amino-propylamino) butane—and to confirm this by synthesis.

For many years I had been interested, with a succession of colleagues, in the action of the base histamine, with its remarkably faithful reproduction of a syndrome occurring in various physiological and pathological reactions, and also caused by the injection of extracts from many animal organs and tissues. A second visit of C. H. Best to my laboratory, primarily for further investigation of a liver extract showing this general type of action, led to the association of Dudley and W. V. Thorpe, who had recently joined him, with Best and myself, in an effort to determine the relation between histamine and the substances causing this action. The chemical side of the work, which was Dudley's direct responsibility, led to the isolation of histamine itself, with relatively large amounts of choline, from the liver extract. The investigation was extended to the

lung, in extracts from which we had been able to demonstrate a very pure and potent activity of the histamine type ; and again histamine was obtained by Dudley and Thorpe, in a yield sufficient to account for all the activity of this type, and under conditions which precluded post-mortem development, or artificial production by the chemical procedures used in its isolation. For the first time we had evidence that this powerful base is a normal constituent of the living cells, and the evidence was extended to other tissues by Thorpe, working by Dudley's methods and with his advice.

One organ had been omitted from this survey of the tissues for histamine, namely, the spleen. When Dudley and I proceeded to fill this gap, he obtained the histamine without difficulty from extracts of the spleens of oxen and horses, by the methods which he had already used with other tissues. We were early met, however, by evidence of an intense activity of the choline type, disappearing very rapidly if the extract was made alkaline and left to stand. The presence of an unstable choline ester in these spleen extracts seemed to be indicated, and it was natural to think of the interesting possibility that it might be acetylcholine. I had earlier worked on the detailed action of this remarkable substance, and Otto Loewi, a few years previously, had shown that a substance having its properties was concerned in the transmission of vagus impulses to the heart. Its great instability made the attempt to separate it from the extract, with the methods then available, a rather uncertain enterprise. Dudley tackled the problem with his usual skill and care, and in due course isolated acetylcholine as the gold and platinum salts, in quantities sufficient for complete chemical identification ; so that acetylcholine, the possible occurrence of which in the body had been the subject of much speculative physiological interest, was demonstrated, beyond question, to be a natural constituent of an animal organ. Incidentally to this investigation, Dudley observed that the chloroplatinate, which crystallizes easily from solutions containing both choline and acetylcholine, is not, as had been supposed, the chloroplatinate of acetylcholine, but a double salt of both bases. He also devised a characteristically elegant method of recovering delicate and unstable bases from their gold and platinum salts.

This discovery of acetylcholine in the animal body, with its physiological implications, aroused wide interest. It was not long before claims were put forward, from a continental laboratory, for the isolation of acetylcholine, in some cases in very large quantities, from practically every organ of the body. Dudley and I eagerly took up the question again, but, at the cost of much fruitless labour, he found himself entirely

unable to confirm these findings. The mystery was only deepened when he visited the laboratory of their origin, confirmed them there, and again consistently failed to reproduce them by exactly the same methods in his own. His gentle nature disliked and shrank from controversy; and even by those who may regard the scientific point at issue as still undecided, I believe that his statement of his observations under these different conditions would be accepted as perfect in its courtesy and its quiet candour.

The last research which Dudley brought to publication was that which resulted in the isolation and description of a new alkaloid from ergot, "ergometrine," the properties of which indicate that it is likely to be accepted as the essential active principle of that remarkable drug, in relation to its principal and traditional use in obstetrics and gynaecology. The clinical experiments of Chassar Moir had given clear evidence of the existence, in watery extracts of ergot, of a substance having a very prompt and powerful stimulant action on the uterus when administered by the mouth. This did not correspond with any of the alkaloids or other active substances which ergot had hitherto yielded; and Dudley, in 1932, embarked upon an attempt to isolate the substance responsible for this action, with the close co-operation of Chassar Moir, who submitted Dudley's preparations to a clinical test at every stage. Various circumstances delayed progress, and by the time Dudley had the alkaloid in his hands, with clear evidence that it was the substance for which they were seeking, workers in other centres were hot on the trail. His publication in March of this year, in which he gave a preliminary description of the alkaloid and named it ergometrine, was quickly followed by other claims to its discovery and to the right to name it. The discovery and its sequel came at a time when Dudley was suffering from the deepest of personal tragedies. Marred though it was by his dread of controversy, the refuge from sorrow which he found in the interest of his new discovery, and in the work still needed to bring it to his own high standard of perfection, enabled Dudley to keep his outward placidity and to finish what he had in hand. His completed description of ergometrine was sent for publication shortly before his fatal illness, and was published in the *Proceedings of the Royal Society* on October 3, the day of his death.

Apart from his services to Biochemistry through his own researches, Dudley did a great deal of quiet and effective work for his colleagues in that branch of science, as Secretary of the Biochemical Society (1922-24), as co-editor, with Professor Harden, of the *Biochemical Journal* (1924-30), and as editor of the biochemical section of *Chemical Abstracts* for the

Chemical Society. He was elected F.R.S. in 1930, and was a member of the Sectional Committee on Physiology at the time of his death.

Ever ready to spend his time and his knowledge in helping others, Dudley was an ideal collaborator. Inspection of a list of the writings to which his name is attached, will show how preponderantly he worked in collaboration. In some cases he worked with junior colleagues, who found him an effective and encouraging teacher and leader. A good deal, however, even in his maturity, was done with senior co-workers. I think it would be true to say that Dudley, sure of his technique and always interested in finding methods for tackling problems which had baffled others, was diffident of his own initiative, and worked more happily and with greater confidence when others had taken the responsibility of suggesting a main objective.

Even those who did not know Dudley personally might have been able to form a partial, but not inaccurate, conception of the man from his work. There was a modest elegance and a feeling for perfection in all that he did, which matched with and indeed formed part of a fine character and personality. Tall and graceful, with a ready and charming smile, Dudley was shy of pretension, of volubility, of exaggeration of any kind, and of any display of emotion. One of his closest friends wrote of him recently as "the sanest man I have ever known." He found his holiday recreation in the gentle sport of fly-fishing. I do not remember to have seen him show anger; a half-humorous annoyance was normally his nearest approach to it. Yet his friends knew that he was a man of very deep feeling, and of warm and loyal affections. His marriage to Miss Mary Nettleship, in 1921, brought him great happiness, though the shadow of a coming tragedy was early cast by her illness in 1922. In the years that followed, her repeated failures of health were faced with a buoyant courage, and a perfect devotion to one another. Her death in April of this year, after a long illness, plunged Dudley into a grief which he could not share; but the bravely hidden sorrow had left him too little reserve to meet his own illness, entailing a serious operation, six months later.

H. H. DALE.

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